REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the rejection of the claims.

Claim 56 has been amended to further clarify the claimed invention. The support for the amendment can be found, for example, at page 52, line 4 and lines 10-14 and page 107, lines 10-32.

Claims 78-80 are newly presented, and are supported throughout the specification, including at page 107, lines 10-32, page 145, line 32 to page 146, line 7; and page 120, line 10 to page 121, line 10.

After entry of the amendment, claims 56 and 69-80 will be pending.

Double Patenting

Claims 56 and 69 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 9, and 10 of copending application no. 10/824,075. Applicants acknowledge the rejection and note that the Examiner has agreed to hold the rejection in abeyance until notice of allowable subject matter.

Enablement

Claims 56 and 69-77 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Office Action has several bases for the rejection. First, the Office Action contends that there is no evidence that inhibition of stanniocalcin results in inhibition of angiogenesis. Second, the Office Action contends use of therapeutic antibodies to treat cancer is unpredictable. Third, the Office Action contends pharmaceutical administration of antibodies to treat tumors is unpredictable. Applicants respectfully traverse this rejection.

There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Only a reasonable correlation between the specification and the scope of enablement is required. If all the other factors point toward enablement, the lack of

working examples will not by itself render the claimed invention non-enabled. MPEP § 2164.02. A basis provided in the Final Office Action for rejecting the claims is the alleged lack of a working example. The Examiner asserts objective evidence such as a working example is "critical and necessary" for enabling one skilled in the art to make and/or use the claimed invention. The MPEP, however, specifically states the "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the ground of lack of enablement." MPEP § 2164.02.

Claim 56 as amended is drawn to a method of inhibiting angiogenesis in a tumor, comprising administering to the tumor an effective amount of an antibody or antigen binding fragment thereof that specifically binds and neutralizes a polypeptide comprising an amino acid sequence of SEQ ID NO:76. Claims 69-79 depend from claim 56.

Claim 80 is new and recites a method of inhibiting PMA-induced angiogenesis. PMA is known to activate protein kinase C (PKC). PKC is known to be an important signaling pathway in the initiation and control of angiogenesis, and promoters of PKC, such as PMA, were known to induce angiogenesis. See, for example, Montesano and Orci, 1987, *J. Cell. Physiol.*, 130(2):284-291, Tsopanoglou et al., 1993, *J. Vasc. Res.*, 30(4):202-208, and Tsopanoglou et al., 1994, *J. Vasc. Res.*, 31(4):195-204 (copies enclosed).

A method of inhibiting angiogenesis as described by the specification is enabled, interalia, through the use of the art recognized model of angiogenesis, and has been confirmed by others. As discussed in the response filed on July 15, 2006, one skilled in the art would expect based on Applicants' teachings and the knowledge in the art related to inhibition of angiogenesis with antibody antagonists that treatment with an agent that antagonizes stanniocalcin activity would inhibit angiogenesis. Applicants teach, for example, that neutralizing antibodies to stanniocalcin are useful as therapeutic molecules because they bind to stanniocalcin and thereby inhibit stanniocalcin activity (page 25, lines 17-19). Applicants show expression of stanniocalcin was upregulated in endothelial cells undergoing tube formation. The collagen gels in the angiogenesis tube formation assay were supplemented with PMA. See, for example, specification at page 123, line 27. Zlot et al. confirm that PMA stimulates the release of stanniocalcin from endothelial cells. See, for example, Table 1 in Zlot et al. at page 47655.

In addition, Applicants have shown that stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma vasculature. Stanniocalcin is not expressed in normal vessels. See the specification at page 145, line 32 to page 146, line 7 and Figures 28 and 29. In addition, Zlot et al. confirm that PMA stimulated tube formation stimulates the release of stanniocalcin. The combination of increased expression in endothelial cells, increased expression in tumor tissue and release of stanniocalcin during tube formation provides a reasonable correlation of the relationship of upregulation of stanniocalcin with angiogenesis in tumor tissues. Applicants submit that treating a tumor with an antagonist to stanniocalcin is enabled by this description and working examples and can occur by multiple routes of administration including intratumoral administration.

Applicants' teachings are also confirmed by other research in the field. For example, Filvaroff *et al.* found that overexpression of stanniocalcin 1 in mice leads to an increase in vascularity *in vivo*. In addition, McCudden et al. has shown that STC-1 and its receptor co-localized in breast cancer cells in 91% of cases. (McCudden et al., *Mol. Cell. Endocrinol.*, 213:167 (2004). STC-1 mRNA was detected in breast cancer cells by *in situ* hybridization and correlates with primary tumor size, # of positive lymph nodes and stage of the cancer cell. (Wascher et al., *Clinical Cancer Res.*, 4:1427 (2003)). Stanniocalcin is also induced in human tumor cells cultured under hypoxic conditions. (Lal et al., *J. Natl. Cancer Inst.*, 93:1337 (2001)). Therefore, one skilled in the art would have had a reasonable expectation that neutralizing or antagonizing antibodies to stanniocalcin would be useful for inhibiting angiogenesis in tumors (page 12, lines 23-28 of the specification).

The Office Action continues to maintain that use of therapeutic antibodies to treat cancer is unpredictable. The Office Action, however, fails to provide any explanation or reasoning as to why the claims lack enablement in view of Applicants' rebuttal evidence.

As discussed in the response filed on July 25, 2006, one of skill in the art would reasonably expect that an antibody that inhibits angiogenesis *in vitro* would inhibit angiogenesis *in vivo*. Antibodies that inhibit angiogenesis *in vitro* have been shown to inhibit angiogenesis *in vivo*. For example, anti-VEGF antibodies were known to inhibit angiogenesis both *in vitro* and *in vivo* and have been approved by the FDA for treating cancer. Contrary to the Examiner's assertions regarding Endostatin, a Phase III trial in nearly 500 patients found that Endostatin

delayed disease progression and the government of China approved a modified version of Endostatin to treat non-small-cell lung cancer. *See* Children's Hospital Boston, Endostatin Update, November 2005 (copy enclosed). Therefore, in view of Applicants' teachings and the knowledge in the art related to inhibition of angiogenesis with antibody antagonists, one skilled in the art would expect that treatment with an agent that antagonizes stanniocalcin activity would inhibit angiogenesis.

The Office Action continues to maintain that pharmaceutical administration of antibodies to treat tumors is unpredictable. The Office Action, however, fails to provide any explanation or reasoning as to why the claims lack enablement in view of Applicants' rebuttal evidence.

As discussed in the response filed on July 25, 2006, pharmaceutical administration of antibodies to treat tumors in mammals was not unpredictable and methods for enhancing antibody tumor penetration and biodistribution were known at the time of filing of the present application. For example, Eccles, 2000, *Breast Can. Res.*, 3:86-90 discloses that antibody penetration into solid tumors can be improved by removing the constant (Fc) region and preparing monomeric or dimeric antibody fragments such as Fab, $F(ab')_2$, and scFV. Applicants describe such antibody fragments and methods for making the fragments in the specification, for example, at page 41, lines 28 to page 42, line 18, page 42, line 26 to page 43, line 5, page 88, lines 5-7 and 11-14, and page 90, line 22 to page 91, line 22. In view of the teachings of the specification and the skill and knowledge in the art as evidenced by the art cited in the previous response, Applicants submit one of skill in the art would have reasonably expected that antibodies and fragments thereof that bind stanniocalcin would be useful for inhibiting tumor.

In view of the forgoing, Applicants submit the specification sufficiently teaches how to practice the claimed methods without undue experimentation. Withdrawal of the rejection is respectfully requested.

Request for an Interview

Applicants request an interview with the Examiner and the supervisor.

SUMMARY

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: April 11, 2007

Katherine M. Kowalchyk
Reg. No.: 36,848

23552
PATENT TRADEMARK OFFICE